Precision Oncology in Prostate Cancer:
How new tests and treatments will change outcomes

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Patient 1

- 52 yo healthy male
- High blood pressure, smoker
- No urinary symptoms, sexually active
- PSA has risen from 1.2 ng/ml to 3.7 ng/ml over 1 year

Epidemiology

Estimated New Cases

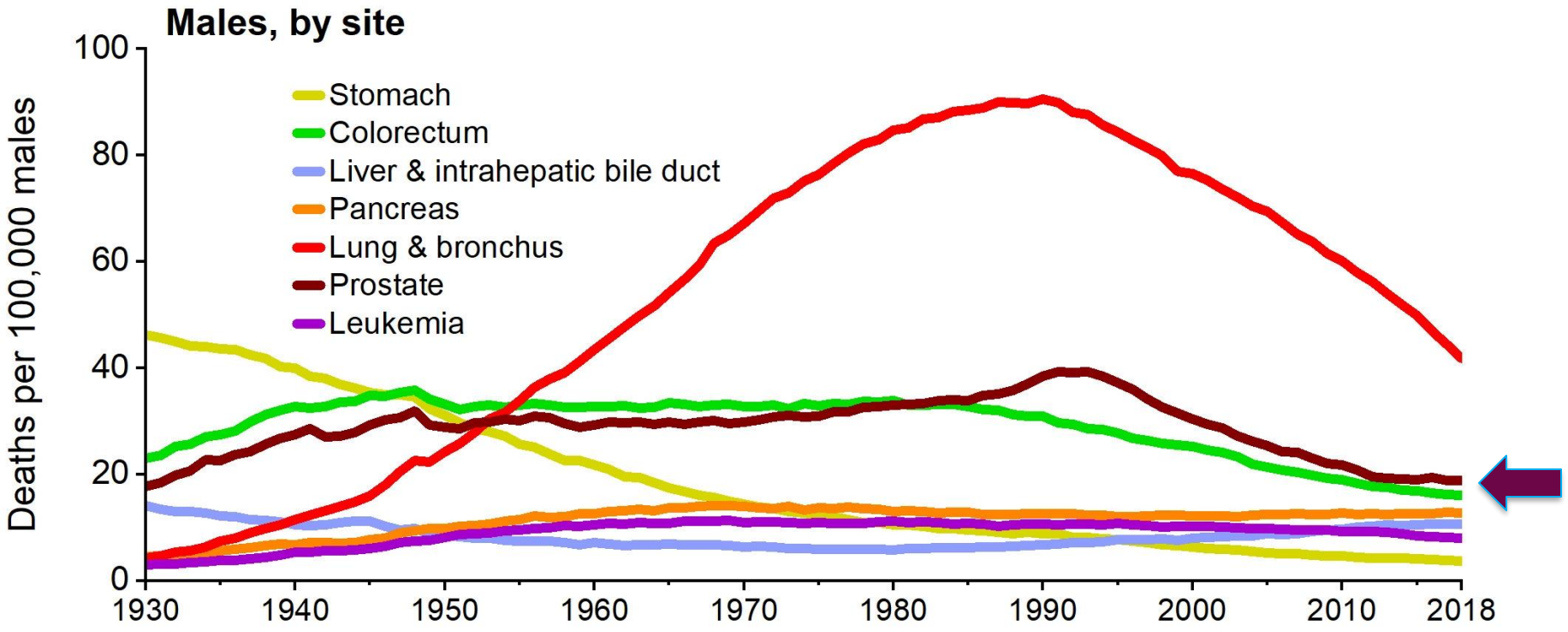
	Males	
Prostate	248,530	26%
Lung & bronchus	119,100	12%
Colon & rectum	79,520	8%
Urinary bladder	64,280	7%
Melanoma of the skin	62,260	6%
Kidney & renal pelvis	48,780	5%
Non-Hodgkin lymphoma	45,630	5%
Oral cavity & pharynx	38,800	4%
Leukemia	35,530	4%
Pancreas	31,950	3%
All Sites	**970,250**	**100%**

Estimated Deaths

	Males	
Lung & bronchus	69,410	22%
Prostate	34,130	11%
Colon & rectum	28,520	9%
Pancreas	25,270	8%
Liver & intrahepatic bile duct	20,300	6%
Leukemia	13,900	4%
Esophagus	12,410	4%
Urinary bladder	12,260	4%
Non-Hodgkin lymphoma	12,170	4%
Brain & other nervous system	10,500	3%
All Sites	**319,420**	**100%**

American Cancer Society 2021

Cancer Death Rates Among Men, US,1930-2018

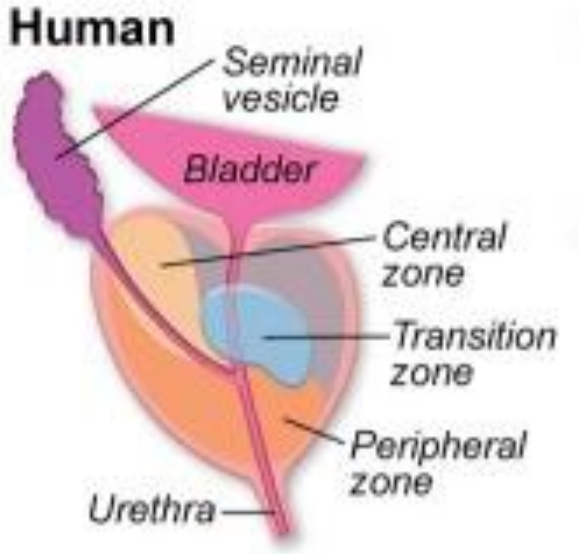


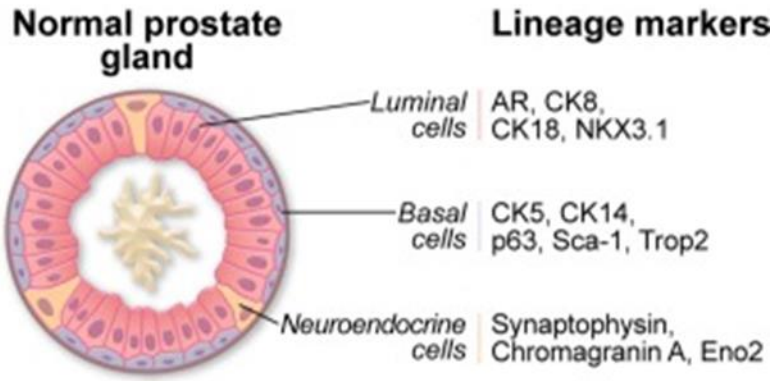
American Cancer Society 2021

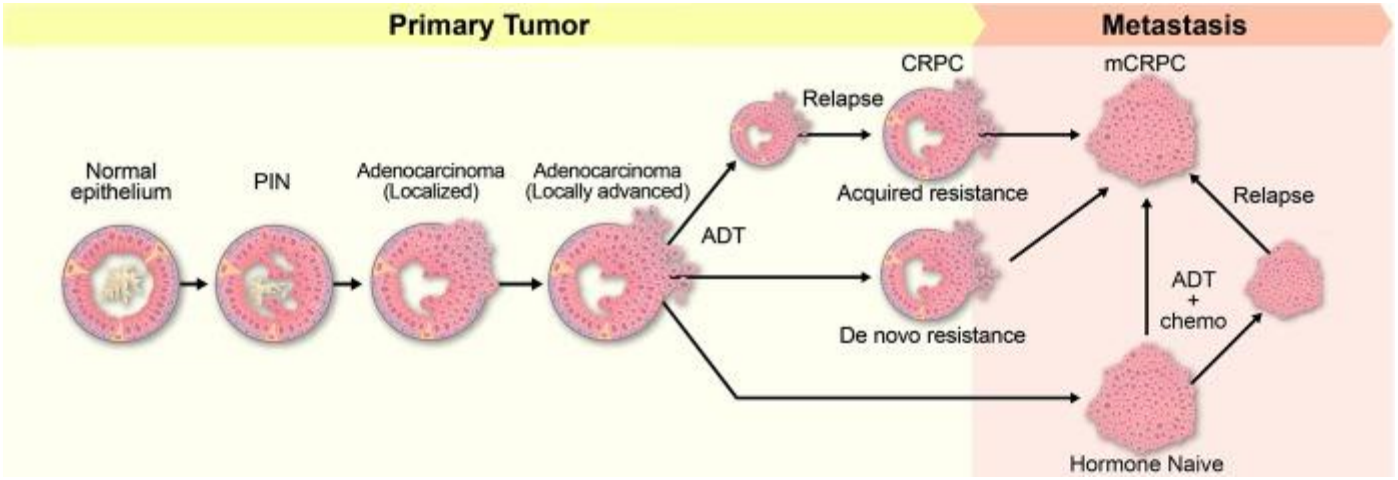
Family History And Risk Of Prostate Cancer

# of Affected First-Degree Relatives	Odds Ratio (95% CI)
1	2.2 (1.4-3.5)
2	4.9 (2.0-12.3)
3	10.9 (2.7-43.1)

Prostate Cancer Screening







Wang Genes Dev 2018

The Quandary Of Prostate Cancer

"Growing old is invariably fatal; prostate cancer is less so."

- Willet Whitmore

“Is cure possible in those for whom it is necessary, and is cure necessary for those in whom it is possible?”

- Willet Whitmore

Conclusions of Randomized Screening Studies

- 2 large randomized trials (US and Europe)
- Significant contamination in US controls
- Survival benefit to screening may increase with time
- Need to consider patient age, relative risks and benefits of screening
- Consider active surveillance more often once diagnosis is made

Is There a "Normal" Cutoff for PSA?

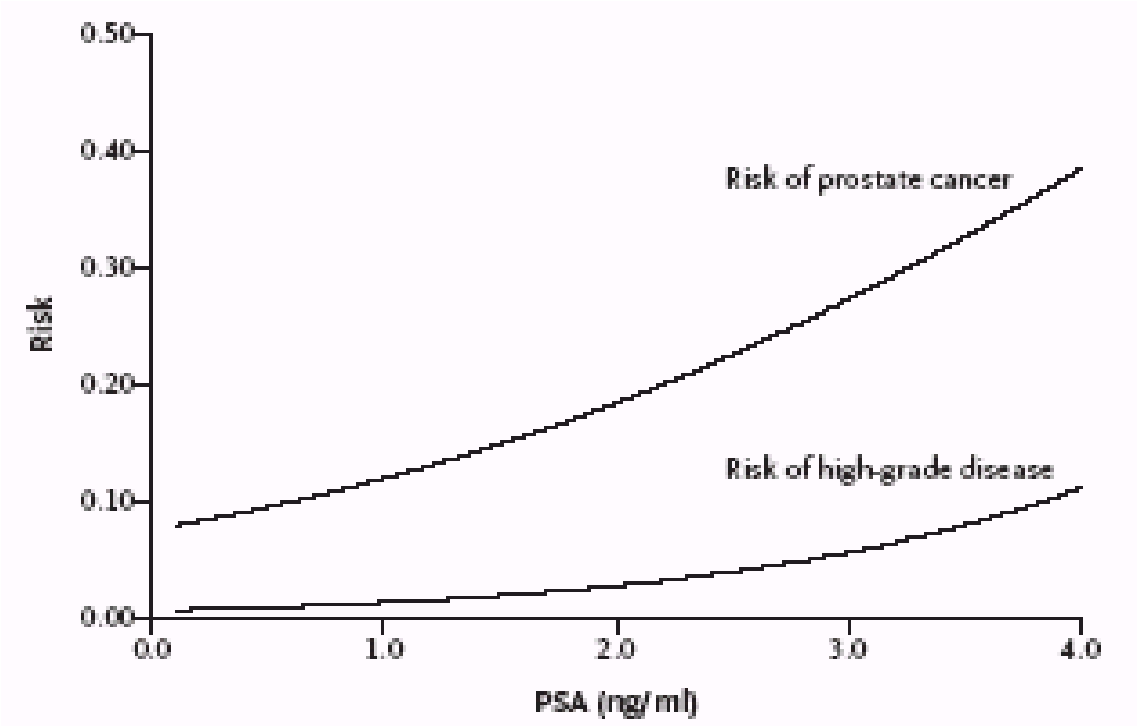


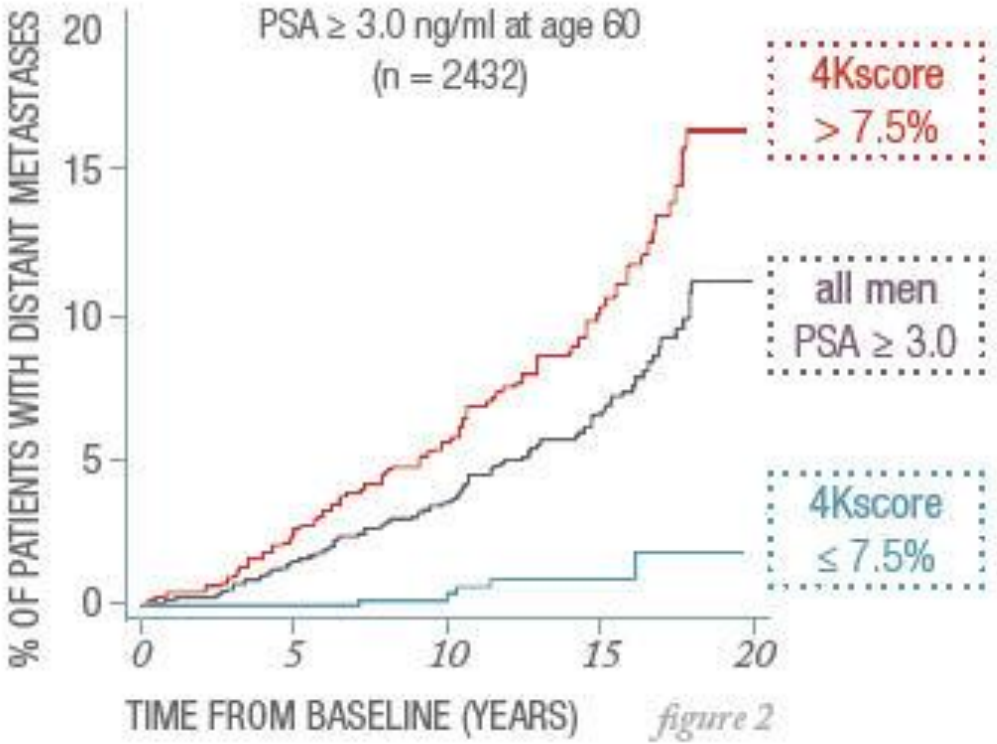
Figure 2. Estimated Risk of Prostate Cancer and High-Grade Disease as a Function of the Prostate-Specific Antigen (PSA) Level.
High-grade disease was defined by a Gleason score of 7 or greater.

Thompson NEJM 2004

Biomarkers to Improve Detection

Test	Specimen	Elevated PSA, considering biopsy	Negative initial biopsy, considering repeat
% free PSA	Blood	X	X
Prostate Health Index (PHI)	Blood	X	X
SelectMDx	Urine	X	
4Kscore	Blood	X	X
ExoDx Prostate Test (EPI)	Urine	X	X
PCA3	Urine		X
ConfirmMDx	Tissue		X

4K Score: Aggressive PC



4Kscore Test Biomarkers
> 7.5% (N = 1510, 62%)

5 year = 2.4%
10 year = 5.6%
15 year = 9.9%
20 year = 16.4%

all men PSA ≥ 3

4Kscore Test Biomarkers
≤ 7.5% (N = 922, 38%)

5 year = 0%
10 year = 0.2%
15 year = 1.0%
20 year = 1.8%

Summary: Screening

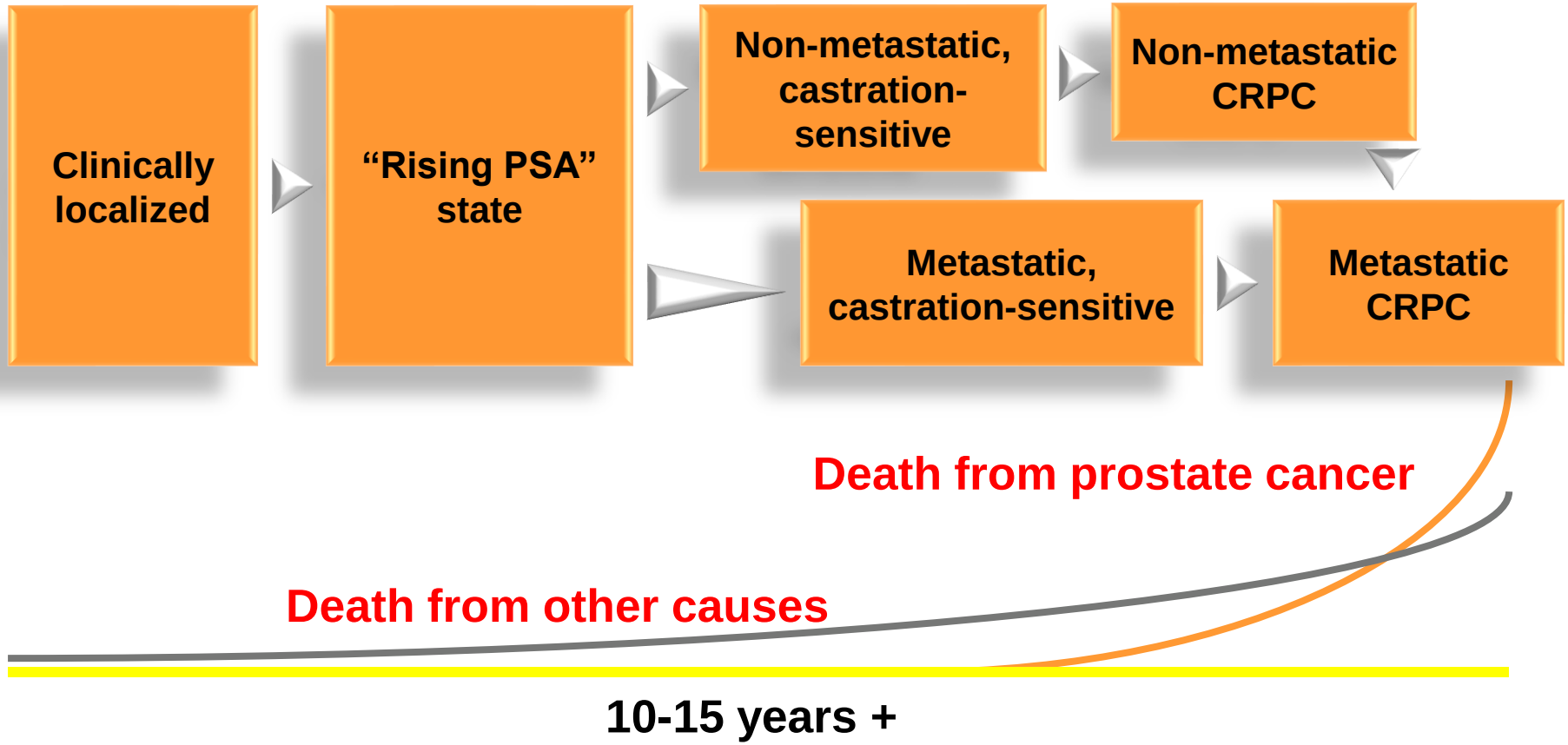
- PSA screening remains controversial but is an option for men 55-69 yrs old
- Randomized trials suggest a modest survival benefit that remains after many years of follow up
- Men with a family history (BRCA+) and AA race are at higher risk and should be offered screening
- Men with life expectancy <10 years should stop screening

Patient 1

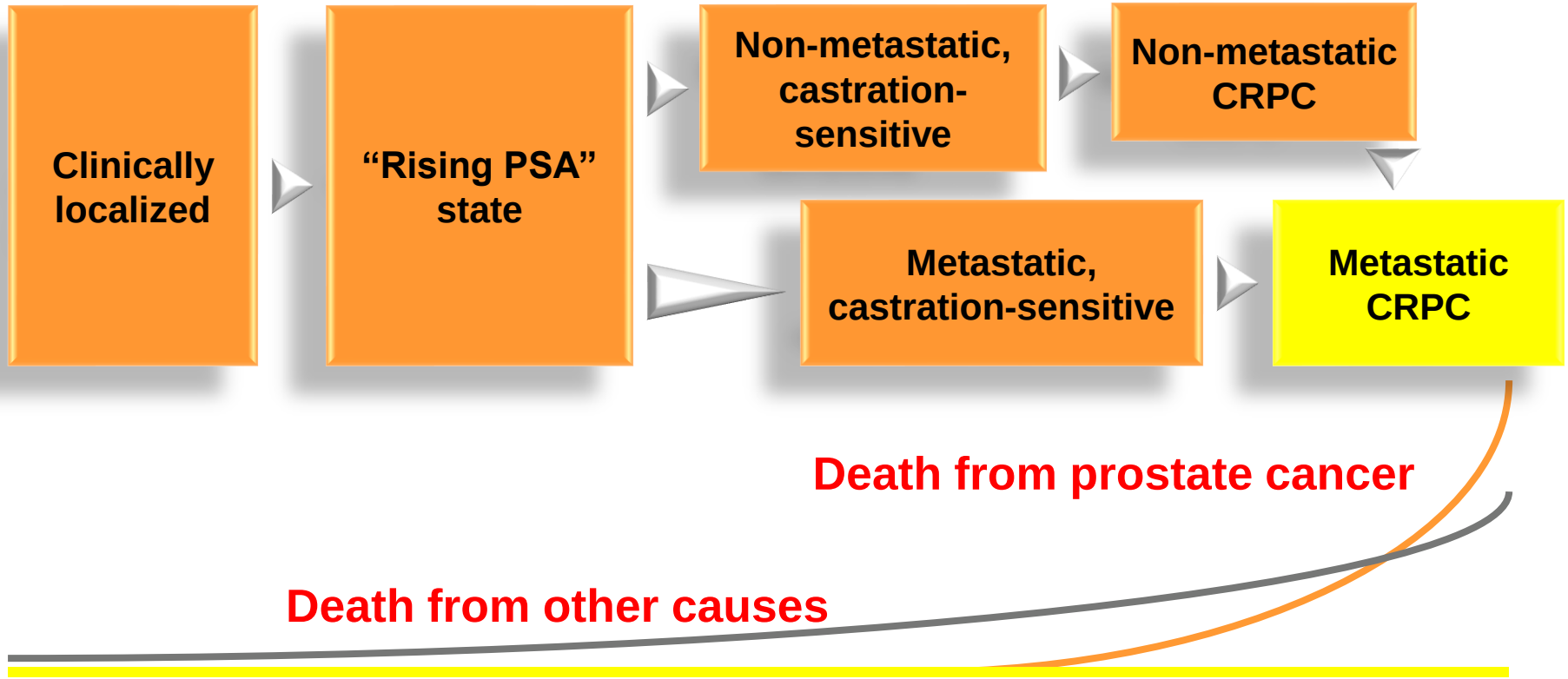
- 52 yo healthy male
- High blood pressure, smoker
- No urinary symptoms, sexually active
- PSA has risen from 1.2 ng/ml to 3.7 ng/ml over 1 year
- Prostate MRI shows 1 cm lesion—fusion biopsy confirms Gleason 3+4 cancer in 1 core.
- Opts for robotic prostatectomy

Advanced Disease

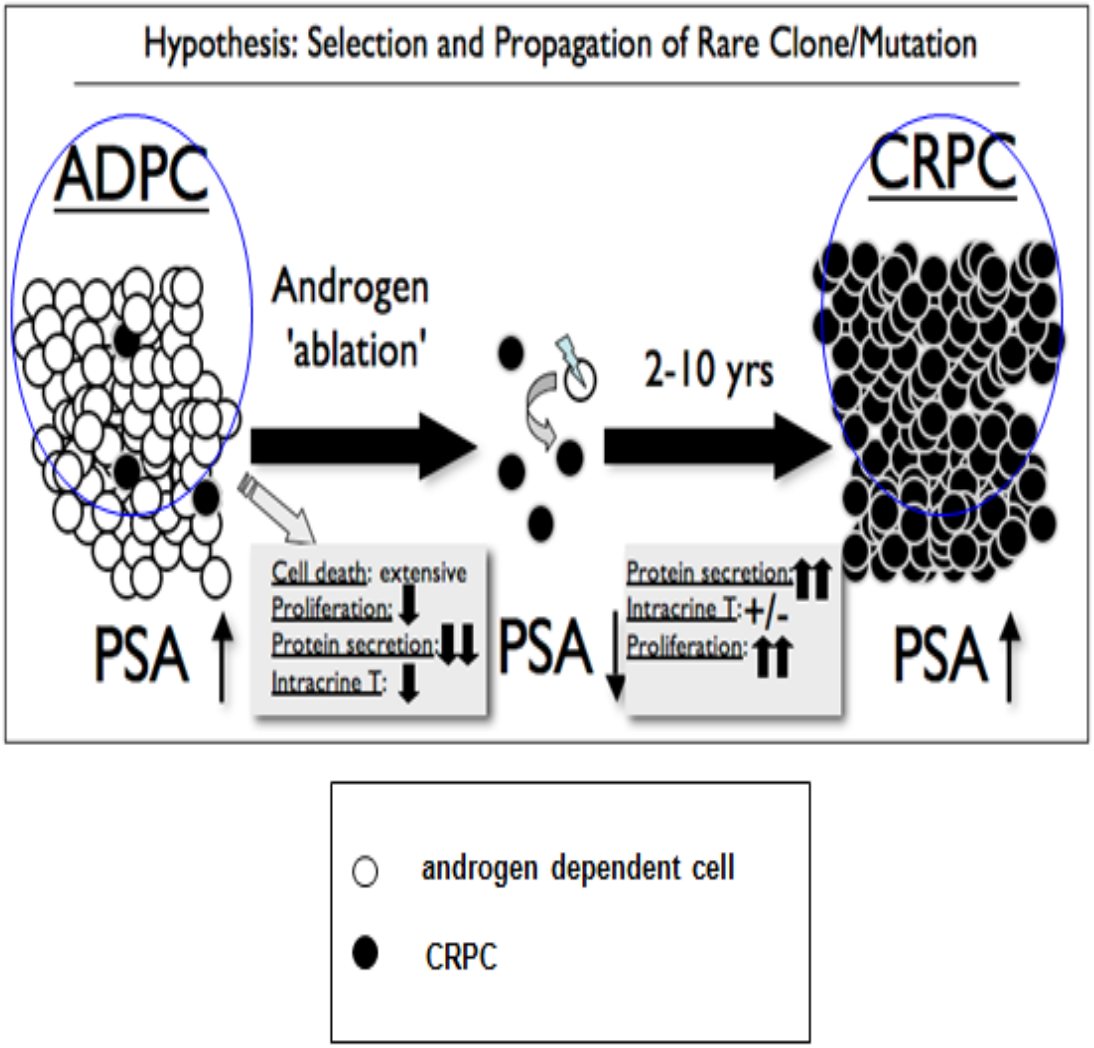
Clinical States of Prostate Cancer



Clinical States of Prostate Cancer



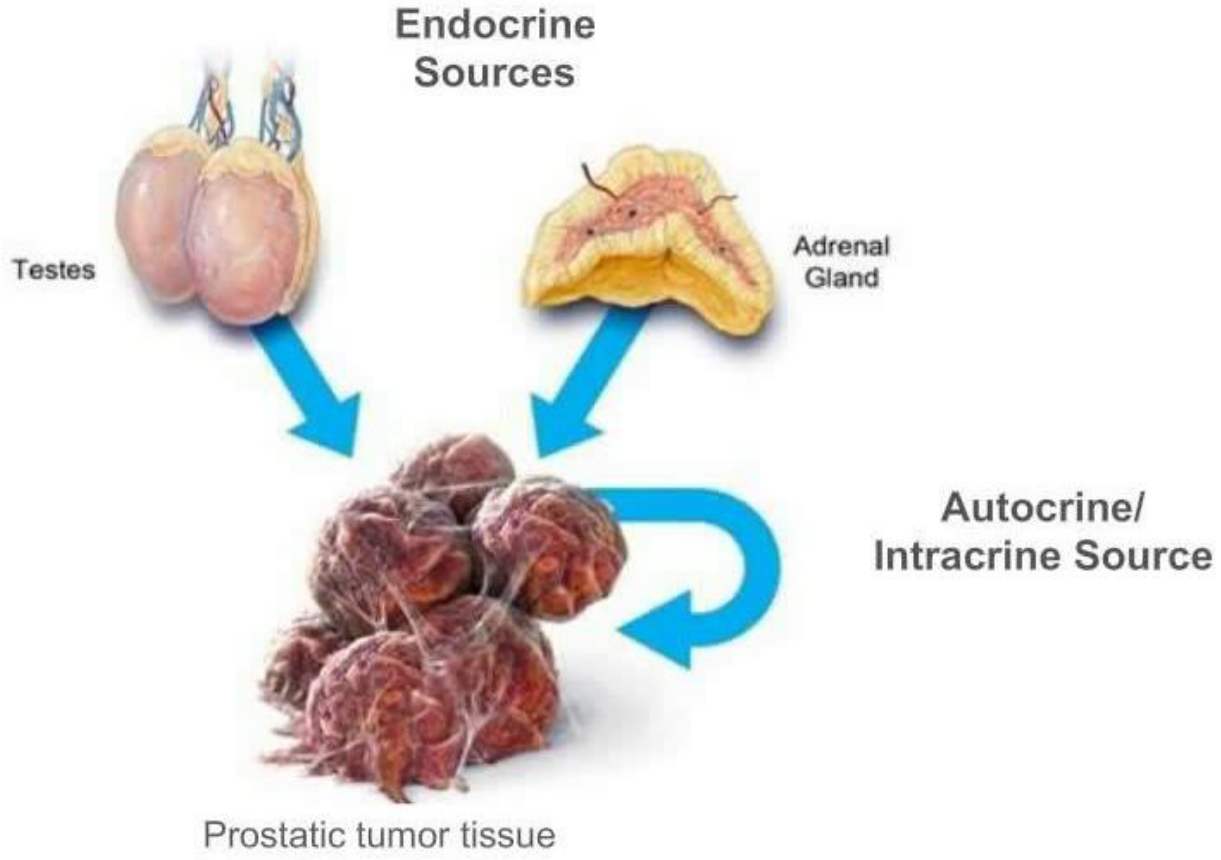
Castration Resistant Prostate Cancer



Positive Trials in mCRPC: OS

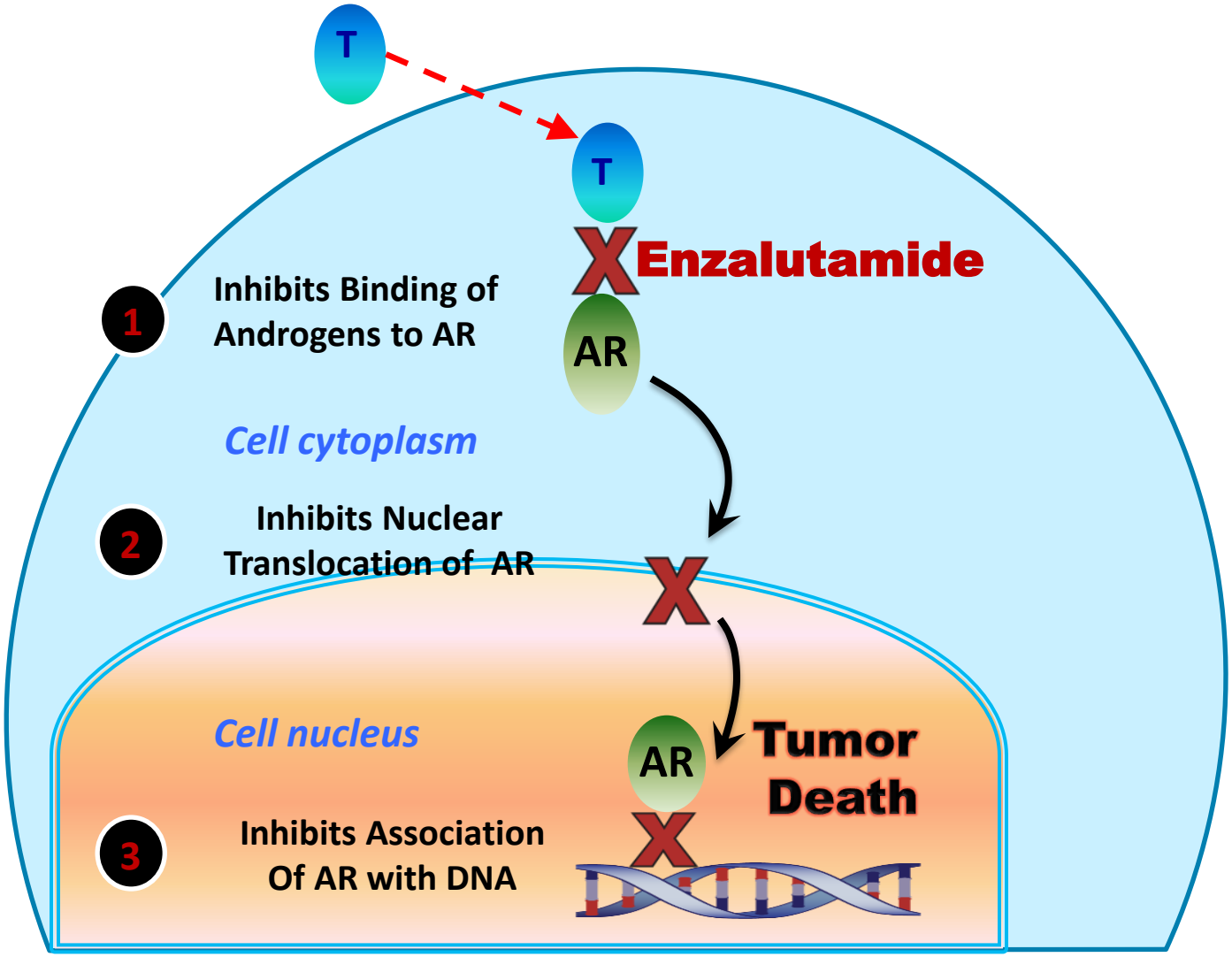
Therapy	Prior Docetaxel	Comparator	Hazard Ratio	P value
Sipuleucel-T	Mostly No	Placebo	0.775	0.032
Docetaxel	No	Mitoxantrone	0.76	0.009
Cabazitaxel	Yes	Mitoxantrone	0.70	<0.0001
Abiraterone/ Prednisone	No	Prednisone	0.81	0.0033
	Yes	Prednisone	0.646	<0.0001
Enzalutamide	No	Placebo	0.706	<0.001
	Yes	Placebo	0.631	<0.001
Radium-223	Mostly Yes	Placebo	0.70	0.002

Three Sources of Androgen



S Nussey and S Whitehead. Endocrinology- an Integrated Approach. Oxford: BIOS Scientific Publishers Limited. 2001
Mostaghel & Nelson, Best Pract Res Clin Endocrinol Metab, 2008 ;22:243-258

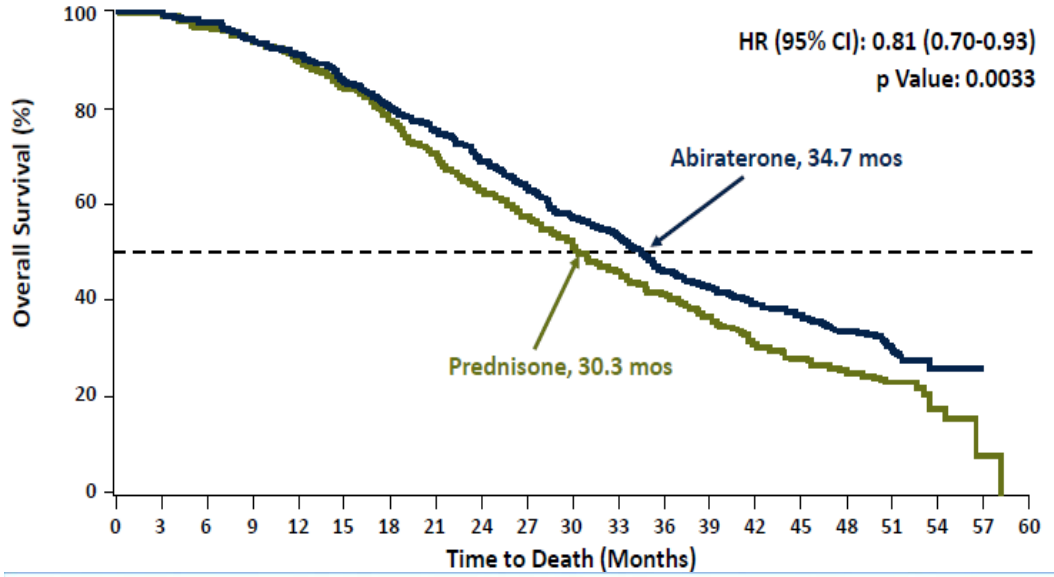
Enzalutamide MOA



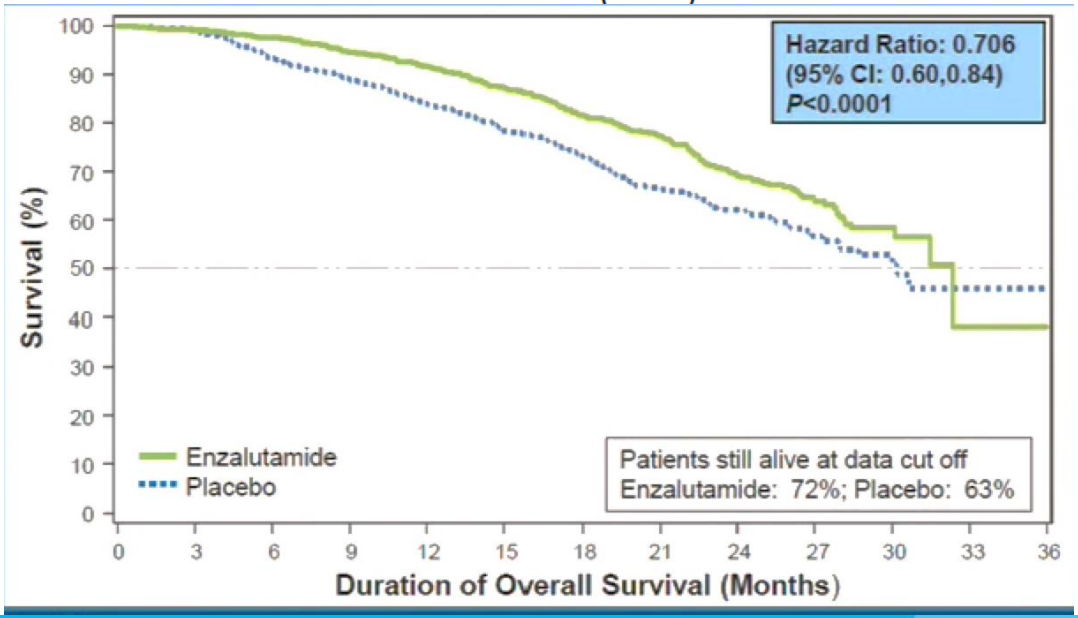
Tran et al. Science 2009;324:787–90.

AR-Targeted Therapies Improve Survival in mCPRC

Abiraterone



Enzalutamide



Targeting Androgen Signaling

- AR targeted therapies improve survival
- Abiraterone and enzalutamide both work
  - Enza has a slightly higher PSA response rate
  - PFS is equivalent and still too short (7.4 mo)
- Certain patients progress more rapidly
  - Liver and lung mets

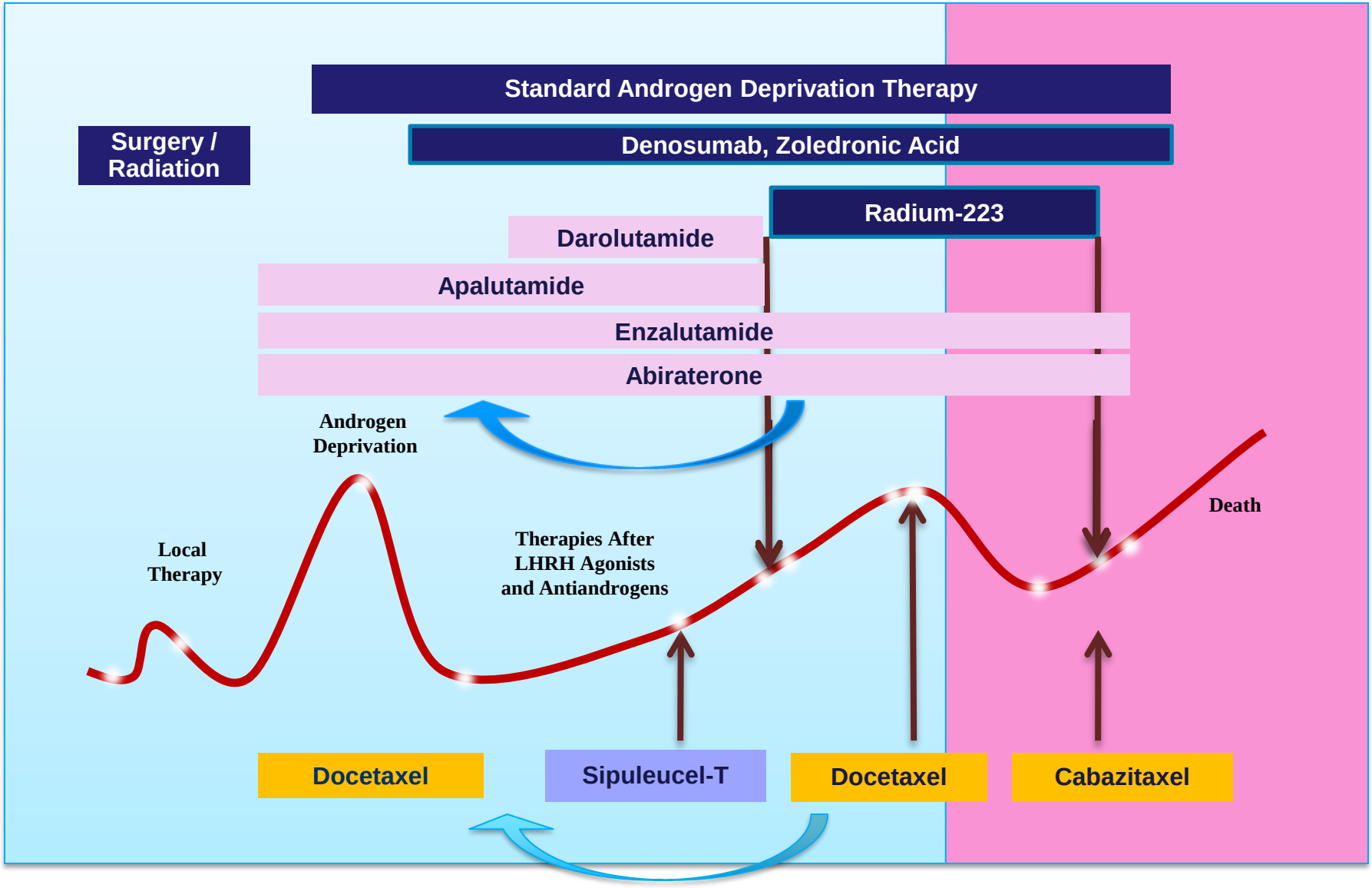
Chemotherapy in mCRPC

- Docetaxel and cabazitaxel remain important therapeutic options in mCRPC

- Need to consider prior therapies in sequencing chemotherapy

- CARD: sequential AR-targeted therapies have less value than 3rd line cabazitaxel chemotherapy in mCRPC

Treatment Landscape



Sema4 Data

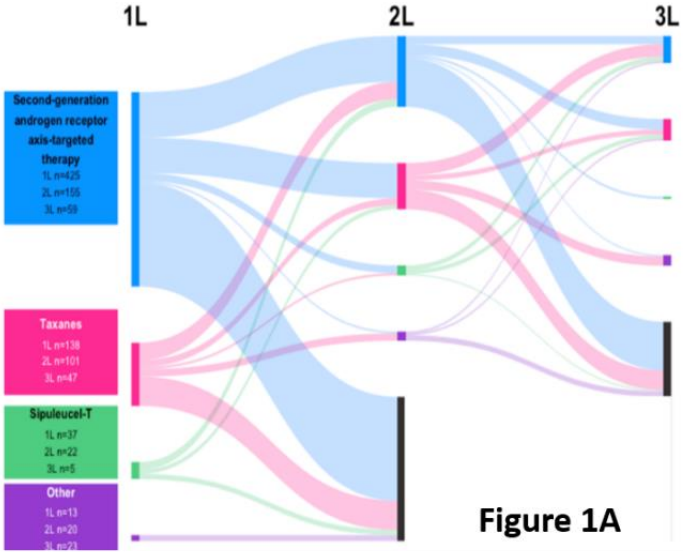


Figure 1A

Flatiron Data

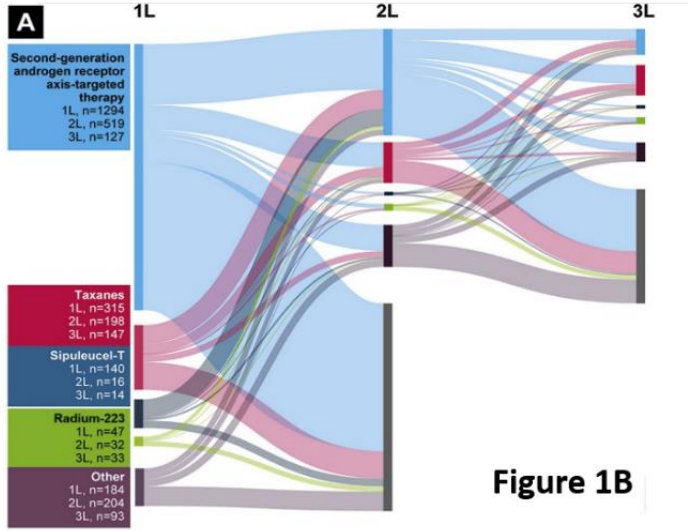


Figure 1B

Treatment for Metastatic Prostate Cancer is Heterogeneous

Patient 2

- 74 yo M with metastatic prostate cancer
- FH: mother with breast cancer at 37 yrs
- PSA 150, bone mets seen on bone scan
- Treated with Lupron, Zytiga/prednisone
- PSA starts rising→docetaxel chemotherapy→progresses after 2 mo

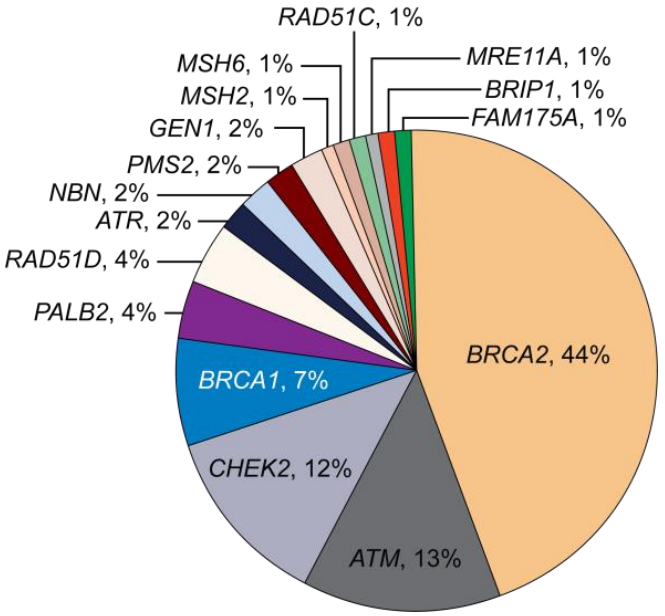
BRCA2 and Other DDR Mutations


THE
ANGELINA
EFFECT
Angelina Jolie's double mastectomy puts genetic testing in the spotlight. What her choice reveals about calculating risk, cost and peace of mind
BY JEFFREY KLUGER & ALICE PARK

DNA Repair Gene Alterations Are Common in Metastatic Prostate Cancer[1,2]

- **23%** of mCRPCs harbor DNA damage repair (DDR) alterations
- The frequency of DDR mutations increases with disease progression

- **About half of these (~12%)** have germline alterations in DDR genes
- Age and family history do not affect mutation frequency



1. Robinson D et al. *Cell*. 2015;161:1215-1228. 2. Pritchard CC et al. *N Engl J Med*. 2016;375:443-453.

Paired Germline and Somatic Testing

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Transforming the Delivery of Cancer Care

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Testing for Both Germline and Somatic Mutations in Prostate and Other Cancers: Impact on Treatment Decision Making

By William Oh, MD

June 24, 2021

ORION by VieCure
Volume 2, Issue 1

Paired Germline & Somatic Testing: Rationale

There is a growing realization that pathogenic mutations can drive cancer growth and represent excellent targets for therapeutic intervention in cancer patients. Driver mutations have been identified in many tumors and are considered somatic or acquired mutations that represent damage that occurs to an individual patient's cells during her lifetime. These mutations are not inherited and are not present in every cell in the body.

In contrast, germline mutations are typically less common and can cause hereditary cancer. These account for 5-10% of all cancers, and >50 hereditary cancer syndromes have been described, including Lynch Syndrome and BRCA1 and BRCA2-Associated Hereditary Breast and Ovarian Cancer.

More recently, prostate cancer has been recognized to be associated with homologous recombination repair (HRR) genes including BRCA1 and BRCA2. As it turns out, metastatic castration-resistant prostate cancer patients may harbor HRR mutations up to 20-25% of the time, divided equally between somatic and germline mutations.1 Such a high prevalence rate was a surprise initially but was likely due to the fact that across all stages of prostate cancer, both germline and somatic pathogenic mutations in HRR mutations are much lower and because testing for such mutations has been uncommon.

Sema4 Signal™

Data-driven Precision Oncology

Cancer Whole Exome Sequencing

- Sema4 is the only company with a commercial laboratory to be approved in all 50 US states for WES/WTS for solid and hematologic malignancies utilizing tumor-normal analysis
- Delivers clinically actionable information about somatic and germline alterations in solid tumors and blood cancers

>99%

Sema4 Signal PanCancer & Sema4 Signal WES/WTS can detect >99% of mutations associated with FDA-approved therapies, standard-of-care treatments, and investigational therapies in clinical trials[5]

Sema4 Signal Whole Exome/Whole Transcriptome Sequencing (WES/WTS)

Captures data from ~18,500 genes to provide the most comprehensive picture of a patient's cancer

Sema4 Signal PanCancer

Captures data from ~18,500 genes to provide the most comprehensive picture of a patient's cancer

Sema4 Signal™

Data-driven Precision Oncology

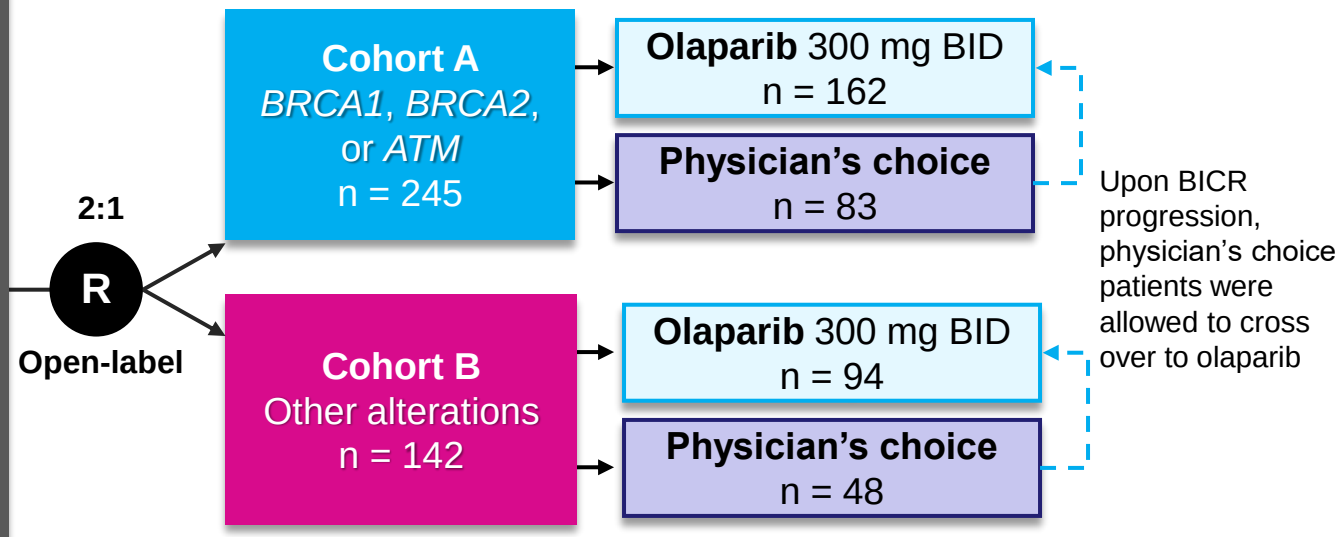
Hereditary Cancer Testing

Comprehensive	17 testing panels, including a 112 gene universal panel and organ-specific sub-panels, run on medical exome data
Accessible	Proactive genetic counseling, best-in-class service, broad network coverage, and digital tools help make testing accessible for providers and patients
Advanced	Multiple methods of analysis ensure the highest detection rates, delivered via the Sema4 Traversa™ genomic platform with biobanking to support future testing

PROfound: Olaparib in DDR Mutant mCRPC

Key Eligibility Criteria
- mCRPC with disease progression on prior NHA (eg, abiraterone or enzalutamide)
- Alterations in ≥1 of any qualifying gene with a direct or indirect role in HRR

Stratification Factors
- Previous taxane
- Measureable disease

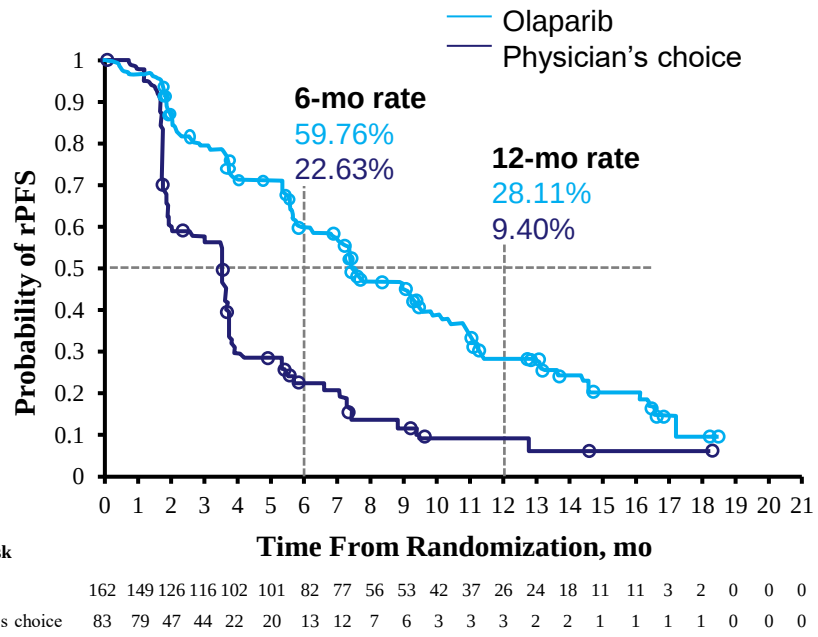


- **Primary endpoint:** rPFS in cohort A (RECIST 1.1 and PCWG3 by BICR)
- **Key secondary endpoints:** rPFS (cohorts A+B); confirmed radiographic ORR in cohort A; time to pain progression in cohort A; OS in cohort A

de Bono J et al. *N Engl J Med.* 2020;382:2091-2102.

PROfound Primary Endpoint: rPFS (Cohort A)[1,2]

rPFS by BICR in Patients With Alterations in *BRCA1*, *BRCA2*, or *ARM* (Cohort A)

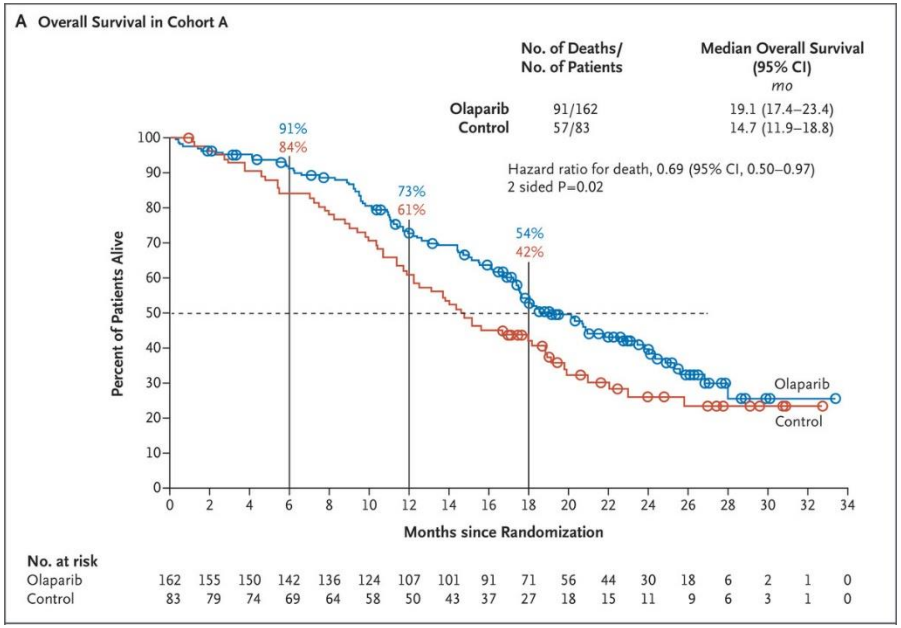


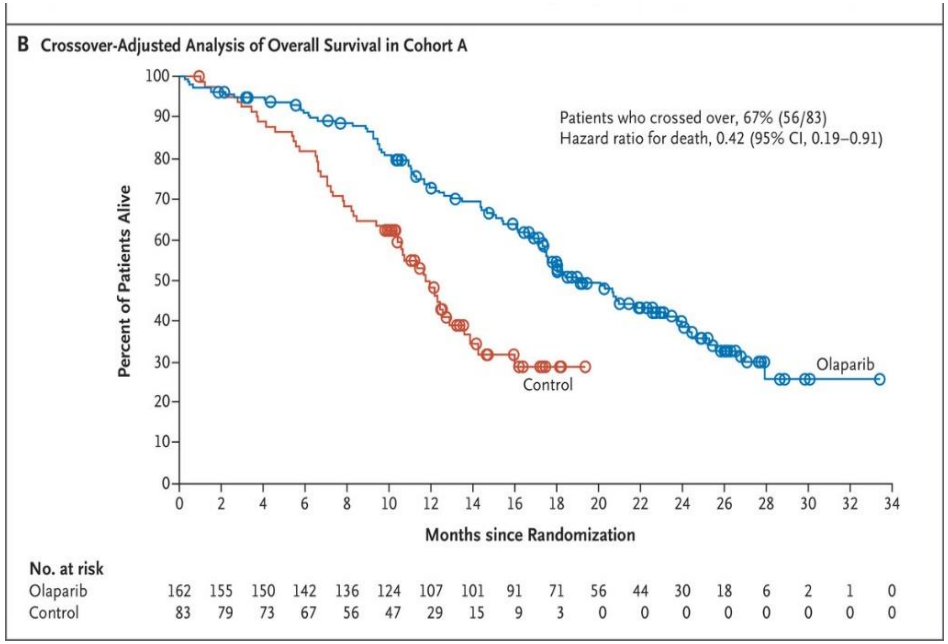
	Olaparib (n = 162)	Physician's Choice (n = 83)
Events, %	106 (65.4)	68 (81.9)
Median PFS, mo	7.39	3.55
HR (95% CI)	0.34 (0.25-0.47) *P* < .001	

NCT02987543
Prespecified sensitivity analysis based on investigator assessment:
HR = 0.24 (95% CI, 0.17-0.34); *P* < .0001

1. Hussain M et al. European Society for Medical Oncology Congress 2019 (ESMO 2019). Abstract LBA12_PR.
2. de Bono J et al. *N Engl J Med.* 2020;382:2091-2102.

PROfound: Updated OS





Despite a 67% crossover rate in the placebo arm, men receiving olaparib with BRCA1/2 or ATM mutations had a significant improvement in OS (HR 0.69 but adjusting for crossover, HR 0.42)

Hussain M et al. *N Engl J Med*. 2020 Sep 20. doi: 10.1056/NEJMoa2022485

FDA Approval: Olaparib for mCRPC

In May 2020, based on data from the PROfound study, the FDA approved olaparib for the treatment of patients with pathogenic germline or somatic homologous recombination repair[a] gene-mutated mCRPC, who have progressed following prior treatment with enzalutamide or abiraterone[1,b]

[a] *BRCA1, BRCA2, ATM, BARD1, BRIP1, CDK12, CHEK1, CHEK2, FANCL, PALB2, RAD51B, RAD51C, RAD51D, RAD54L*.
[b] Select patients for therapy based on two FDA-approved companion diagnostic tests: BRACAnalysis CDx and FoundationOne CDx.
1. https://www.fda.gov/drugs/drug-approvals-and-databases/fda-approves-olaparib-hrr-gene-mutated-metastatic-castration-resistant-prostate-cancer.

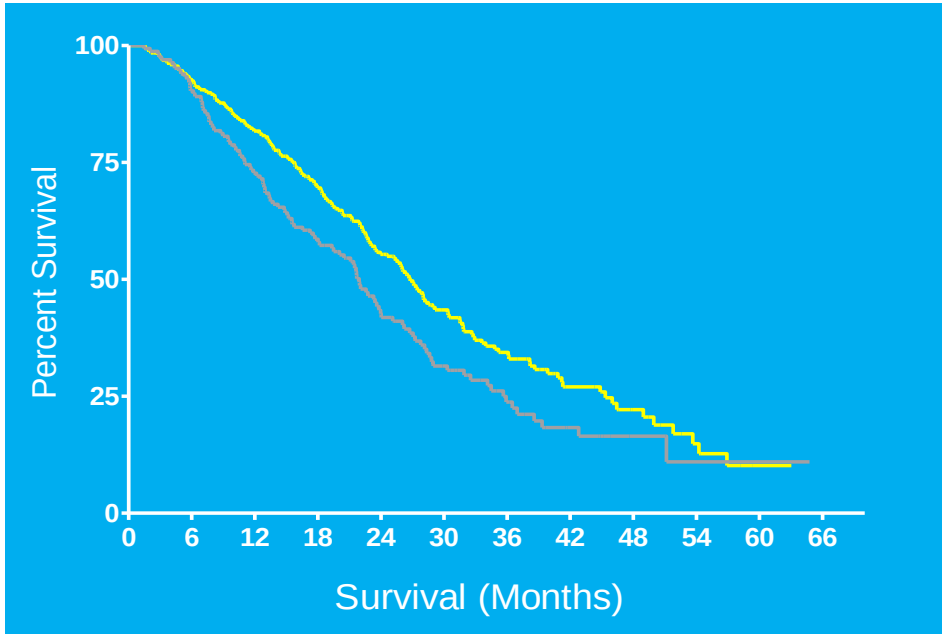
Patient 2

- 74 yo M with metastatic prostate cancer
- FH: mother with breast cancer at 37 yrs
- PSA 150, bone mets seen on bone scan
- Treated with Lupron, Zytiga/prednisone
- PSA starts rising→docetaxel chemotherapy→progresses after 2 mo
- Genomic testing on tumor shows BRCA2 mutation and he starts on olaparib

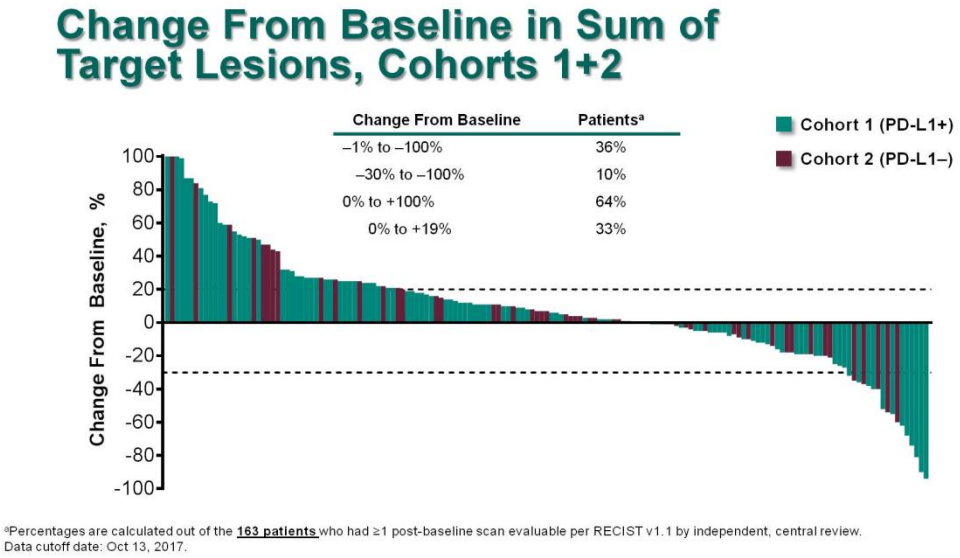
Immunotherapy?

Sipuleucel-T Survival Benefit

- Sipuleucel-T was approved based on HR 0.775 (~4 month OS benefit)
- Survival curves separate after 6 months
- Treatment is done in 5 weeks
  - Few side effects

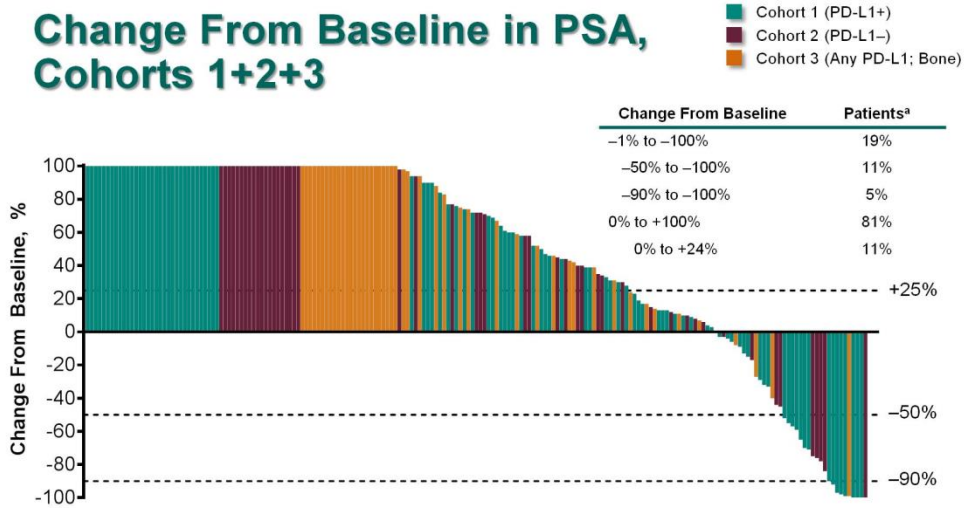


Pembrolizumab in mCRPC



[a]Percentages are calculated out of the 163 patients who had ≥1 post-baseline scan evaluable per RECIST v1.1 by independent, central review.
Data cutoff date: Oct 13, 2017.

10% RR



[a]Percentages are calculated out of the 193 patients who had ≥1 post-baseline PSA assessment.
Data cutoff date: Oct 13, 2017.

11% PSA declines

Antonarakis et al J Clin Oncol. 2020 Feb 10;38(5):395-405.

COSMIC-021: Cabozantinib + Atezolizumab

Figure 1. Cabozantinib Targets Pathways Associated With Tumor Immune-Suppression

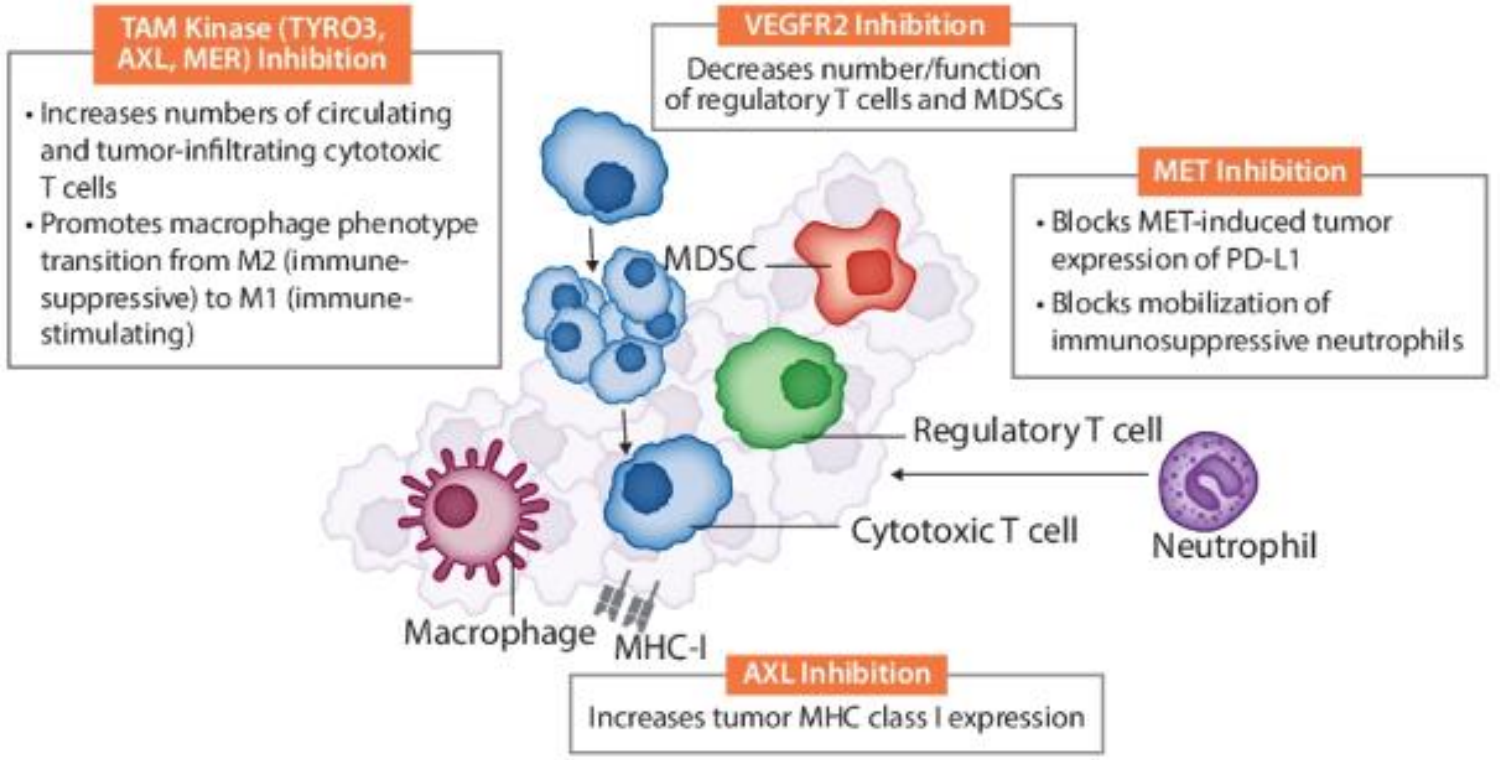
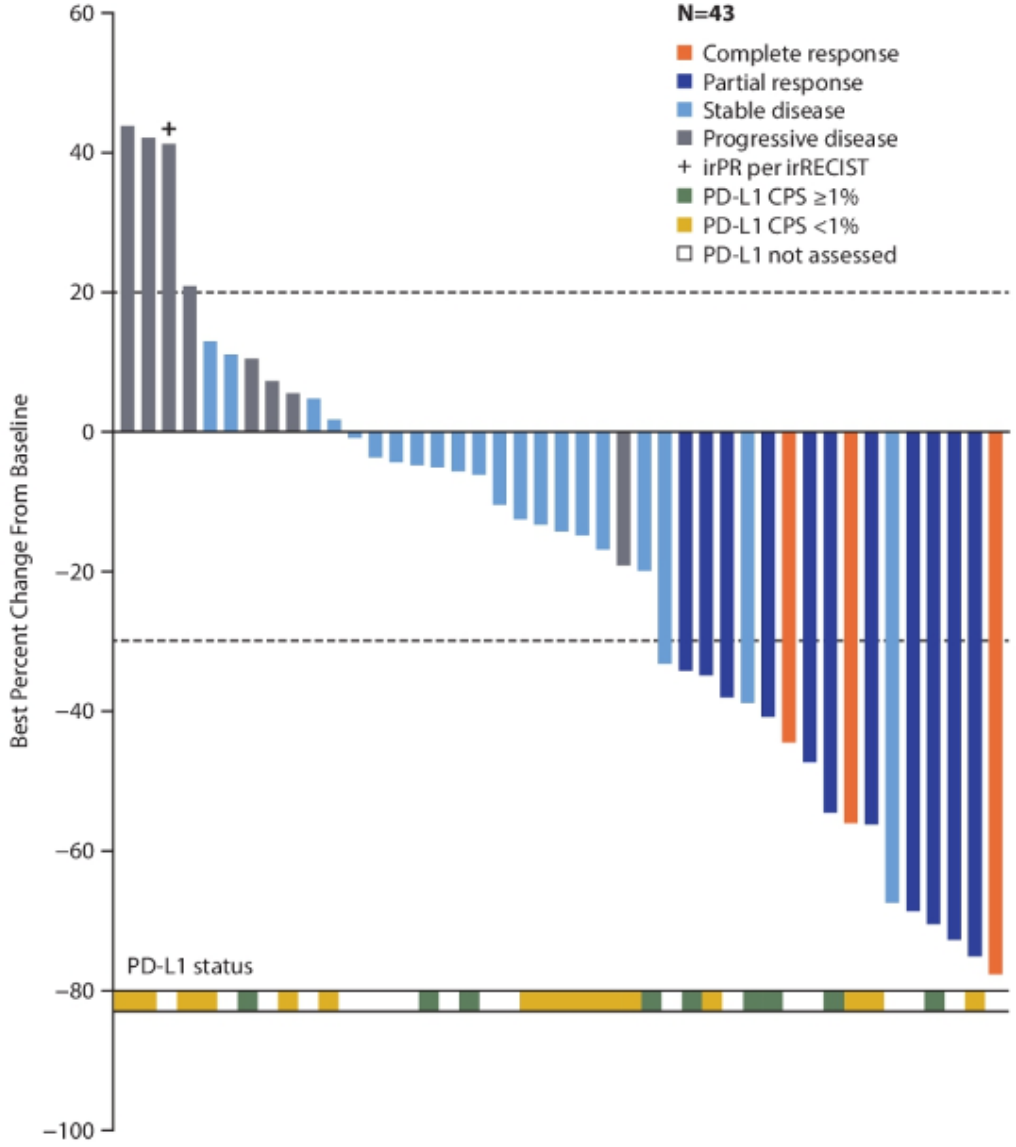


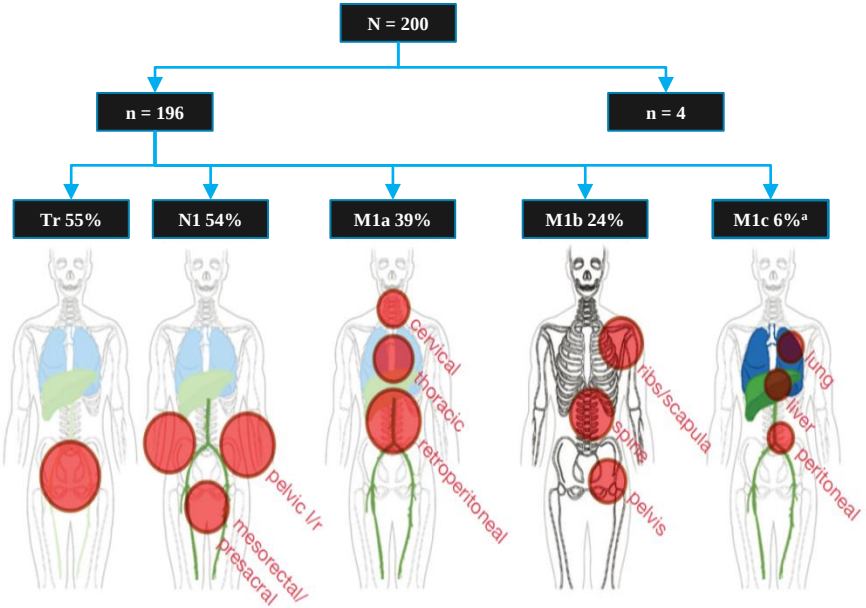
Figure 3. Best Change From Baseline in Sum of Target Lesions per Investigator by RECIST v1.1



43 out of 44 patients had at least one post-baseline tumor assessment. The three patients with CRs had lymph node metastases as target lesions; one patient (notated above) had an irPR per irRECIST with a reduction in target lesions from baseline of ~60% after initial PD (see **Figure 4** for change in target lesions with time). PD-L1 status is shown for patients with known PD-L1 status; analysis of PD-L1 is ongoing.

PSMA-Directed Therapy

PSMA-PET Results in Patients With High-Risk nmCRPC (Negative Conventional Imaging, PSADT <10 mo)[1]



The size of the red circle is proportional to lesion prevalence.

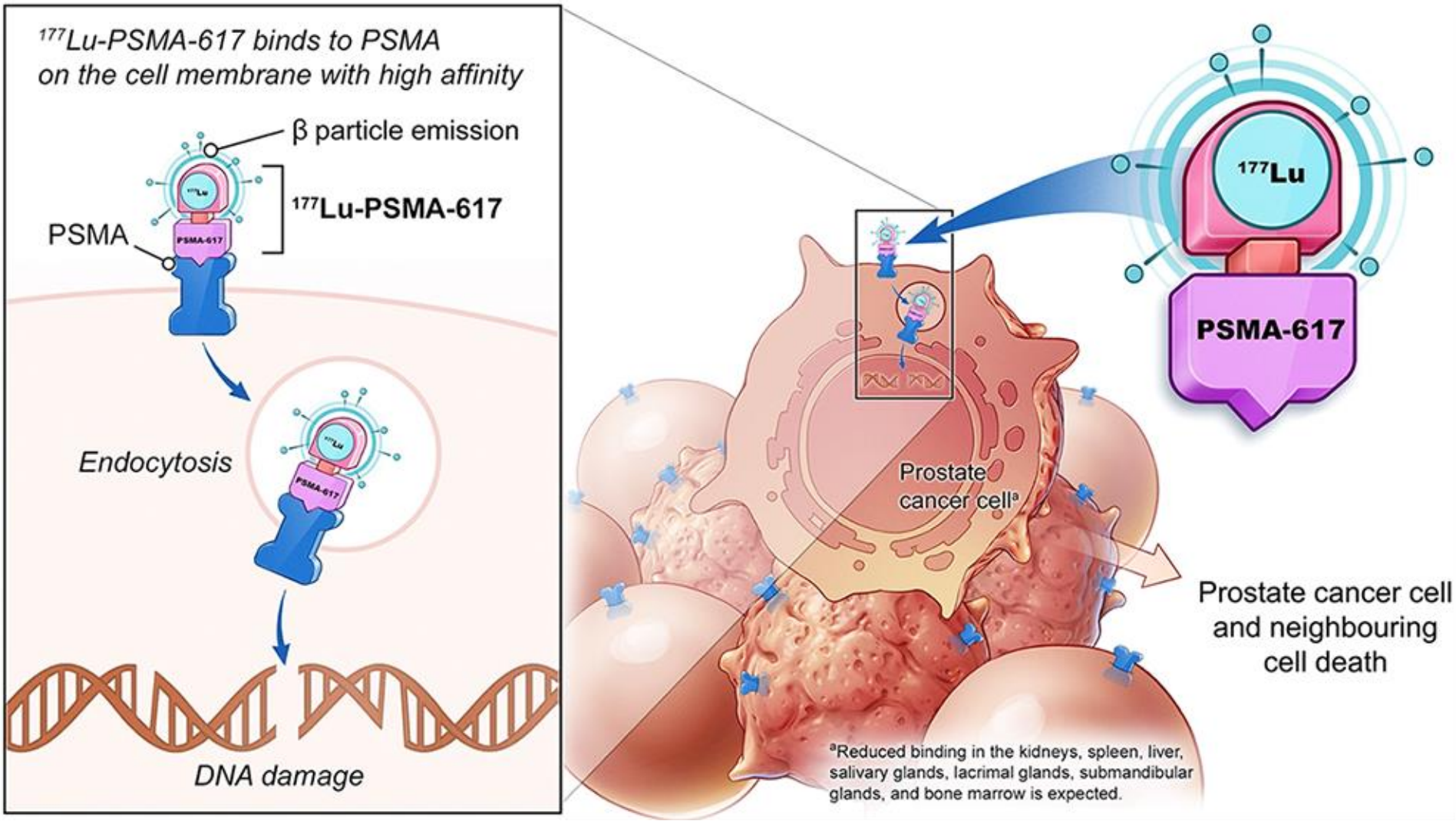
PSMA-PET was positive in 196 of 200 (98%) patients; 55% of patients had any distant metastatic disease

Category Based on miTNM Stage, n (%)	All patients (N = 200)
M0	**91 (46)**
T0N0M0 (no PC lesion)	4 (2)
TrN0M0	48 (24)
T0N1M0	13 (7)
TrN1M0	26 (13)
Any M1	**109 (55)**
T0N0M1	31 (16)
T0N1M1	42 (21)
TrN0M1	9 (5)
TrN1M1	27 (14)
N/M disease extent	
Unifocal (1 lesion)	29 (15)
Oligometastatic (2-3 lesions)	28 (14)
Multiple/disseminated (≥ 4 lesions)	91 (46)

[a] Lung (n = 4), liver (n = 5), peritoneum (n = 4), connective tissue (n = 1).

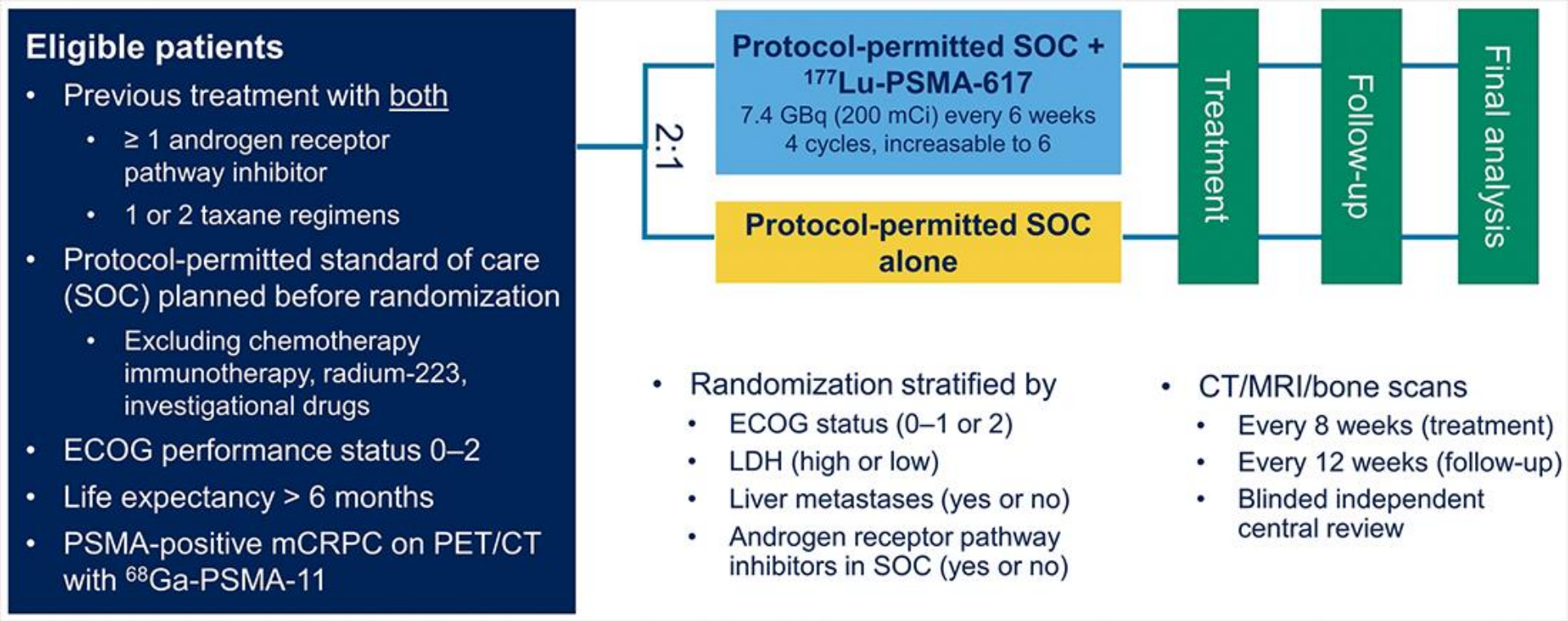
1. Fendler WP et al. *Clin Cancer Res*. 2019;25:7448-7454.

Phase 3 VISION Trial



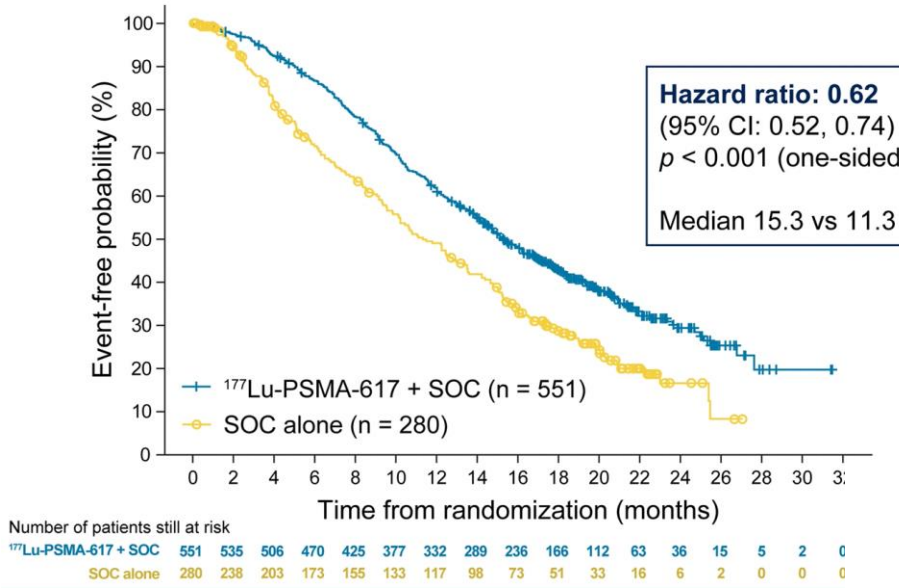
Morris M et al. ASCO 2021 Plenary

Phase 3 VISION Trial



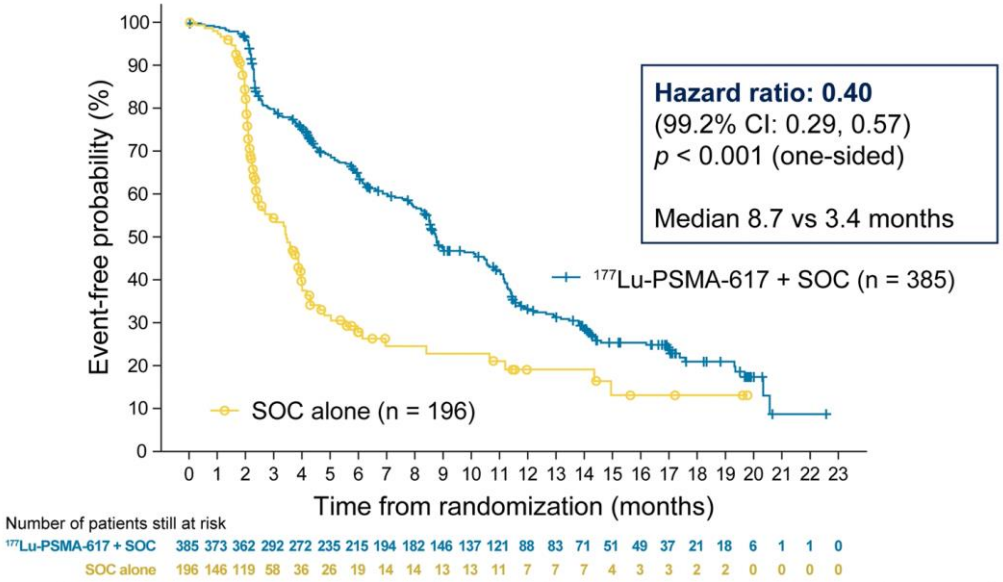
Morris M et al. ASCO 2021 Plenary

Phase 3 VISION Trial



Overall survival

Progression-free survival



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New Therapies in mCRPC

- PARP inhibitors have significant clinical activity in mCRPC in patients with BRCA2 and other DDR mutations
- Novel immunotherapy combinations and biomarker analyses may lead to broader use of immunotherapy
- PSMA-targeted therapies show significant activity and will likely be FDA approved